

بسم الله الرحمن الرحيم
In The Name Of ALLAH
The Most Gracious, The Most Merciful



Armed Forces College of Medicine

AFCM



Anti-psychotic Drugs

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INTENDED LEARNING OBJECTIVES (ILO)

By the end of this lecture you will be able to:

1. Classify first generation antipsychotic drugs.
2. List the pharmacological actions and therapeutic uses of Chlorpromazine
3. Explain the adverse effects of chlorpromazine
4. Identify the therapeutic uses of Haloperidol & Droperidol.
5. Classify 2nd generation (atypical) antipsychotic drugs.
6. Differentiate the difference between 1st and 2nd generations of antipsychotic drugs in the mechanisms of actions and adverse effects.
7. Identify the mechanisms of action and adverse effects of 2nd generations (atypical) antipsychotic drugs.

Anti-psychotics

(Major Tranquillizers)

(Neuroleptics)

Psychosis

- **Psychosis** is losing contact with reality

A severe mental disorder in which thoughts and emotions are so impaired that contact with external reality is lost.

Symptoms of psychosis:

typically divided into two categories:

Positive symptoms:

They are changes in thoughts and feelings that are " added on " to a person's experiences (e.g., hearing voices).

Negative symptoms:

They are things that are " taken away " or reduced (e.g., reduced motivation or reduced intensity of emotion).

Positive Symptoms: Delusions & Hallucinations

- **Delusions:**

➢ **False beliefs** that **cannot be shaken despite reason or proof to the contrary**.

➢ It is often very difficult for other people to understand why the person holds this belief.

Examples:

1. feeling they are **being watched, followed or monitored in some way**
2. believing they are **being plotted against**
3. believing they **have special abilities or "powers"**
4. convinced that certain sights or sounds are specifically directed towards him

- **Hallucinations:**

- Hallucinations involve **seeing**, **hearing**, **feeling**, **smelling** or **tasting** something that is not actually there.

These experiences **appear entirely real to the person** who is experiencing them.

- The most common type of hallucination **involves hearing things** - such as voices or particular sounds - such as music.

- The content of the voices can **range from friendly to critical, cruel and upsetting and may even tell the person what to do.**

Negative symptoms:

Negative symptoms reflect a decrease in, or loss of, normal functions.

“negative” symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment,

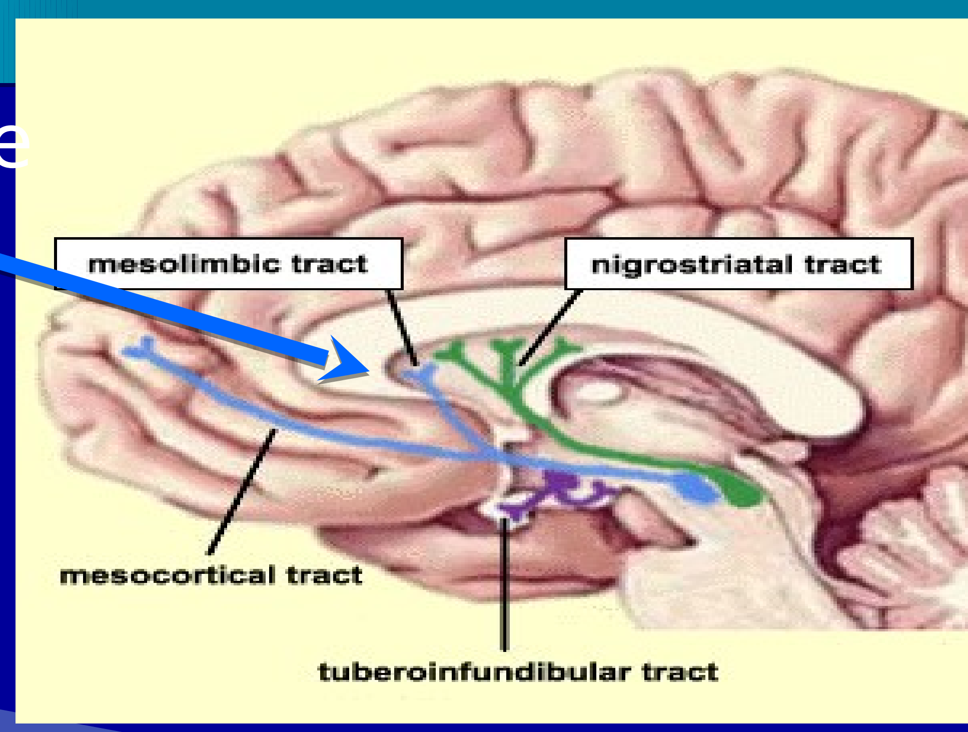
These symptoms are often **less evident than positive symptoms** and require careful assessment.

Psychosis

- Identify pathophysiology of psychosis.
- **Psychosis** has been traditionally linked to

Over activity of dopamine function in the brain

Particularly in the **mesolimbic pathway.**



Most of Anti-psychotics

especially 1st generation

act via

Blocking central D_2 receptor

in hypothalamus and limbic system

First-generation antipsychotics are more likely to be associated with <u>extrapyramidal symptoms (EPS),</u>

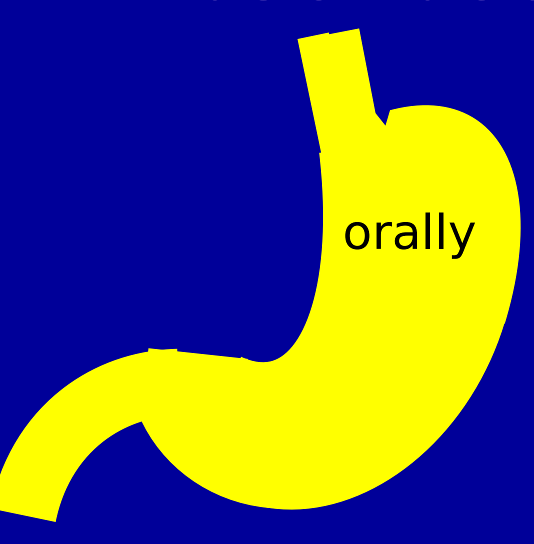
particularly drugs that bind tightly to dopaminergic neuroreceptors, such <u>as haloperidol</u>

FIRST-GENERATION ANTIPSYCHOTIC (low potency)	
Chlorpromazine	THORAZINE
Thioridazine	

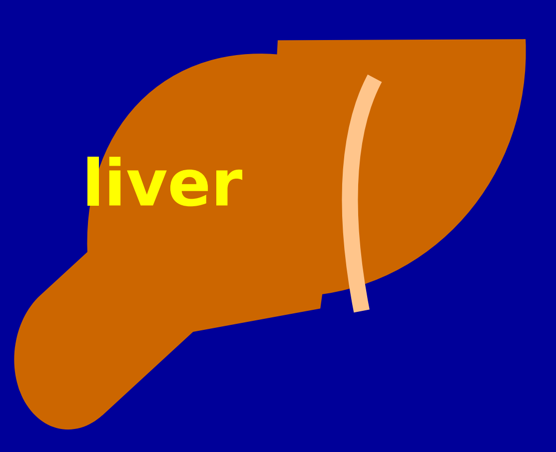
FIRST-GENERATION ANTIPSYCHOTIC (high potency)	
Fluphenazine	PROLIXIN
Haloperidol	HALDOL
Loxapine	LOXITANE
Perphenazine	
Pimozide	ORAP
Prochlorperazine	COMPAZINE
Thiothixene	NAVANE
Trifluoperazine	STELAZINE

1. Chlorpromazine *(Largactil)* Pharmacokinetics:

Absorbed:

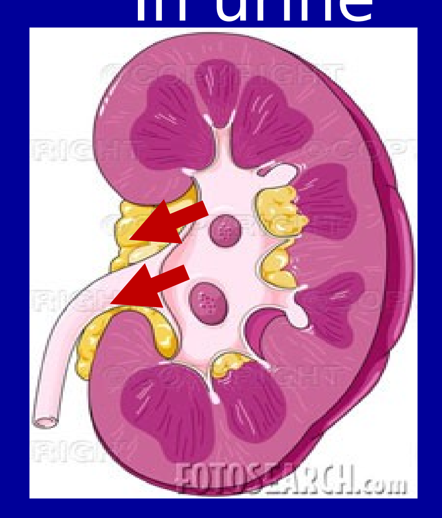


Metabolized:



Excreted:

In urine



Describe the pharmacological actions of Chlorpromazine

hlorpromazine

Actions

1- C. N. S.:

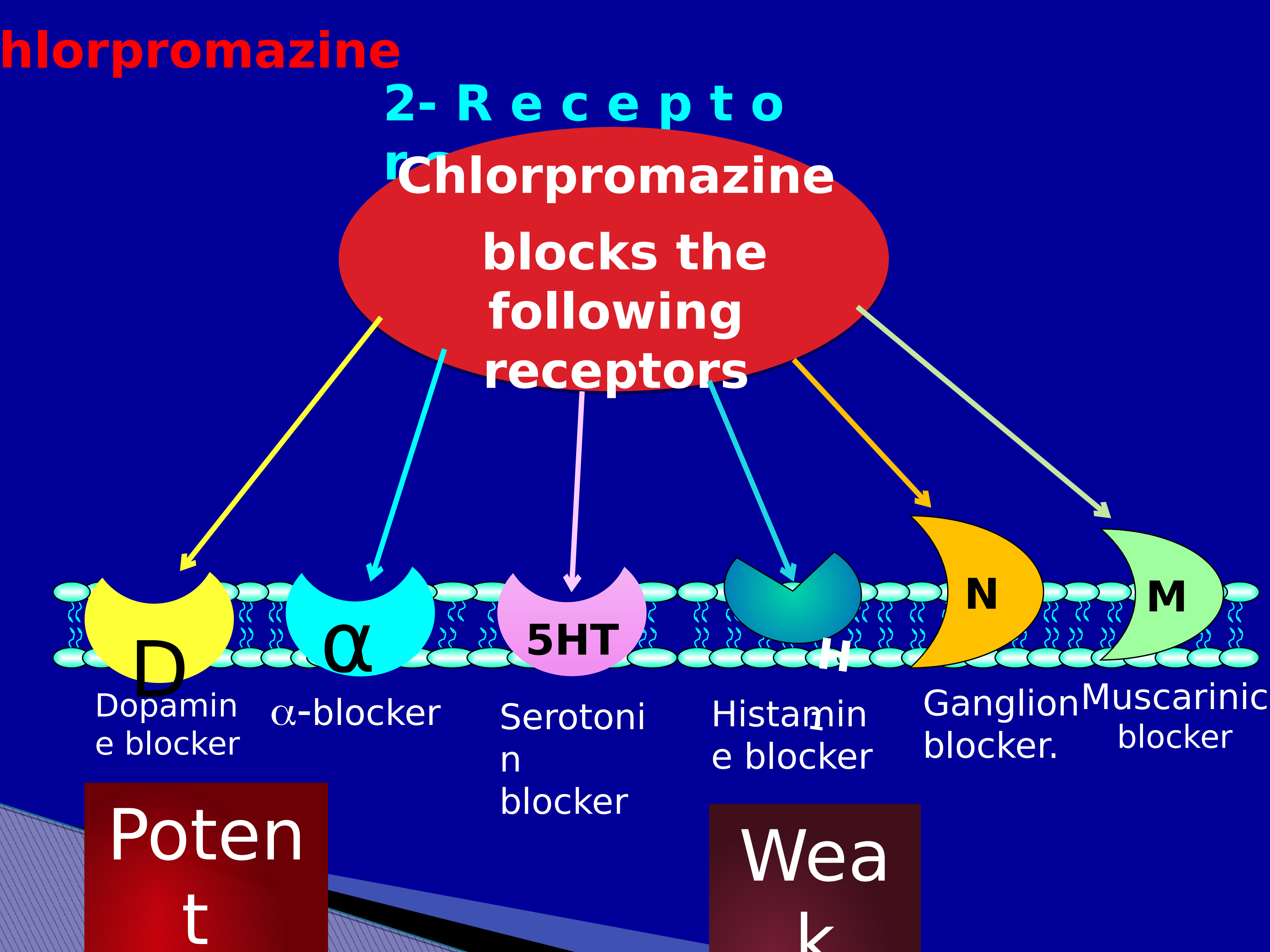
Chlorpromazine blocks Dopamine (D_2) receptor in

The limbic system:
Anti-Psychotic

C.T.Z
Antiemetic

Basal Ganglia
Extrapyramidal symptom
Worsen Parkinsonism

Hypothalamus
- Hypothermia
- ↑ Appetite &
- ↑ Prolactin.

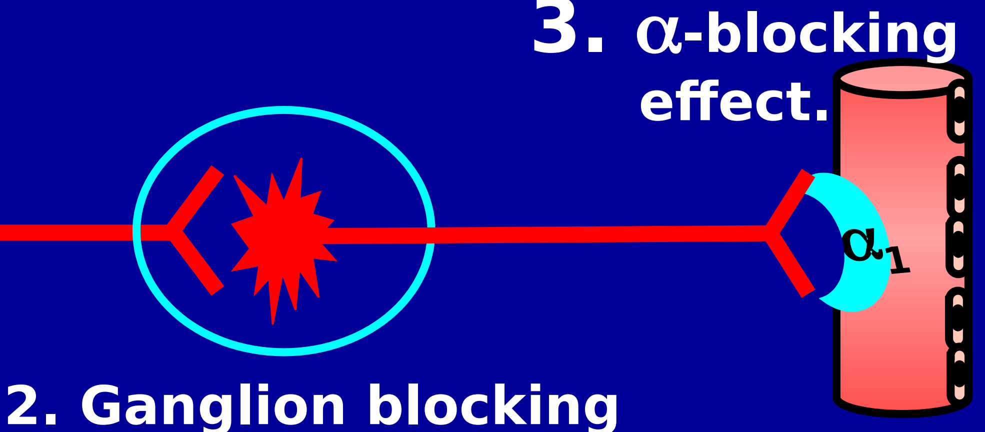


hlorpromazine
2- R e c e p t o r s
Chlorpromazine
blocks the following receptors
D
α
5HT
H
N
M
Dopamine blocker
α-blocker
Serotonin blocker
Histamine blocker
Ganglion blocker.
Muscarinic blocker
Potent
Weak

hlorpromazine

3. C. V. S:

1. Hypotension & Postural Hypotension:



3. α-blocking effect.

2. Ganglion blocking effect.

4. Direct vasodilatation





5. Direct myocardial depression

3. C. V. S:

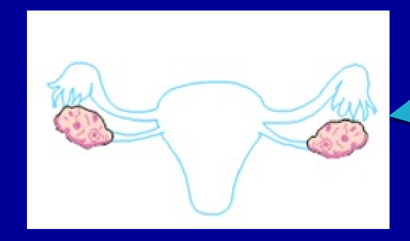
2. Tachycardia:



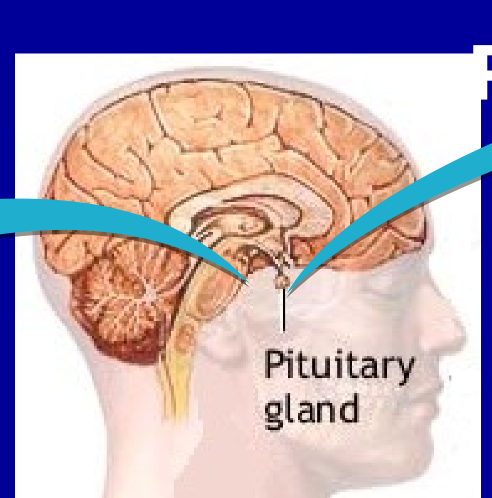
- Atropine like
- Reflex from **hypotension**

4. E n d o c r i n e:

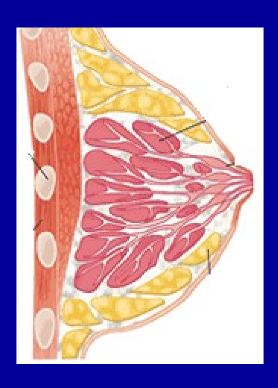
- ↓ FSH & ↓ LH



Infertility



- ↑ Prolactin



Gynecomastia & Galactorrhea

hlorpromazine

st the therapeutic uses of chlorpromazi

herapeutic Uses:

1. **Psychosis e.g. Schizophrenia**

- **can reduce hallucinations and delusions associated with schizophrenia ("positive" symptoms) by blocking D2 receptors in the mesolimbic system of the brain.**

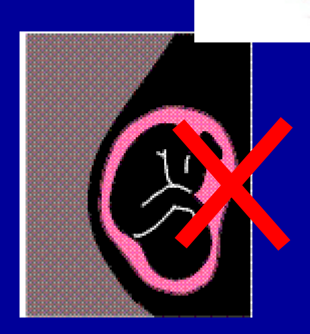
- **The "negative" symptoms, such as blunted affect, apathy, and impaired attention, as well as cognitive impairment, are not as responsive to first-generation antipsychotics.**

- **N.B : Many second-generation agents, such as clozapine, can ameliorate the negative symptoms to some extent**

hlorpromazine

Therapeutic Uses:

2. Anti-emetic Except in:
   - Motion sickness
   - Pregnancy



3. Intractable hiccoug



hlorpromazine

xplain the adverse effects of chlorpromazine

ide Effects

1- C.N.S.:

- Drowsiness & *Sedation(antihistaminic ef*
- Extrapyramidal Manifestations:

1- Dystonia (painful muscle spasm twistir

2- Akathisia (motor restlessness).

3- Parkinsonism(shuffling gait, masked face, M. rigidity)

4- Tardive dyskinesia(involuntary movement of orofascial

Muscles)

- Neurolept-malignant Syndrome:

Idiosyncratic reaction (similar to malignant

Chlorpromazine

Side Effects

2. Atropine like Side Effects:



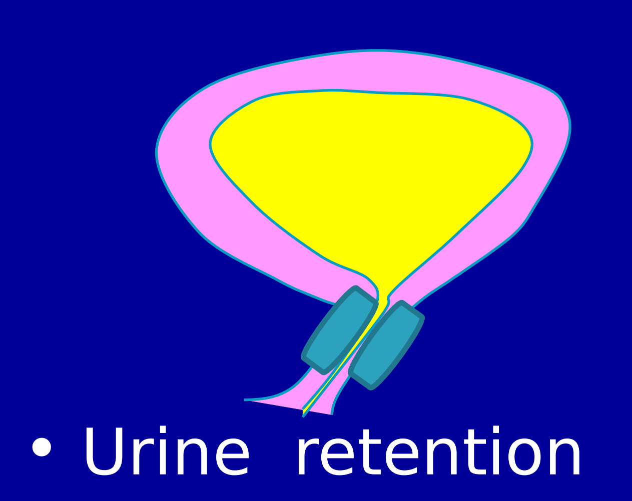
- Dry mouth



- Blurred vision
  & I.O.P



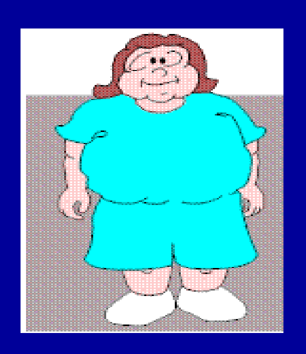
- Tachycardia



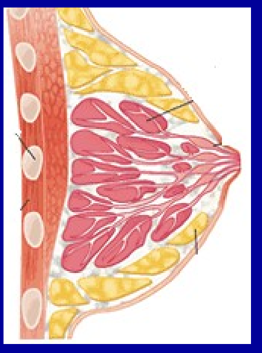
- Urine retention

Chlorpromazine

Side Effects



3. Obesity



4. Gynecomastia , galactorrhea & Infertility



5. Postural hypotension



6. Teratogenic.

1. The typical 1st generation anti-psychotic drugs produce the following side effects except:
   a) Parkinsonism
   b) Tardive dyskinesia
   c) Hypertension
   d) Glactorrhea
   e) Neuroleptic malignant syndrome

entify the therapeutic uses of Haloperidol & Droper

aloperidol & Droperid

Similar to Chlorpromazine

But with Stronger

anti-dopamine effects.

Haloperidol & Droperidol

Uses:

Haloperidol: Anti-psychotic in Schizophrenia.

Droperidol + Fentanyl → I.V. Neurolept Analgesia for minor operations.

The emetic effect of fentanyl is antagonised by the antiemetic effect of droperidol

Differentiate the difference between 1st and 2nd generations of antipsychotic drugs in the mechanisms of actions and adverse .effects

Dopamine relative 5-HT & vice versa

Improve — +ve symptoms

Worsen — -ve symptoms

Meso-Cortical

5-HT -ve symptoms

5 HT

Improve

-ve symptoms

BUT

Worsen

+ ve symptoms

(relative in dopamine)

Meso- Limbic



Dopamine



+ve

II- Atypical Anti-Psychotic Drugs

- More effective in ttt of schizophrenia & Less side effects.

Examples:

A - **Clozapine: It blocks dopamine receptors (D1, D4, weak D2),**

5-HT2, muscarinic & α-receptors

for refractory patients as it produces bone marrow supression

& has high incidence (1-2%) of Agranulocytosis.

Newer atypical antipsychotics do not routinely cause movement disorders.

BUT: weight gain, diabetes, and unfavorable lipid profiles.

- **Clozapine** : blocks **(D1, D4, weak D2), //5-HT2, muscarinic & α- receptors**

  may cause **agranulocytosis** and therefore requires **biweekly blood counts.**

- **Risperidone : blocks 5-HT_{2A} > D2 receptors.**

  ts **active metabolite** has been linked to **QT prolongation**

- **Aripiprazole : partial agonist at D2 and 5-HT1A + blocks 5-HT_{2A} Receptors**

  a drug said to be a **“dopamine stabilizer,”** effective **in some patients who have not responded to other therapies**.

After several failed trials of various antipsychotic drugs, a 46-year-old woman is switched to a new medication for her schizophrenia. However, a few weeks later, she develops pneumonia. A complete blood count is ordered and reveals a significantly reduced number of neutrophils, basophils, and eosinophils. Which of the following agents is the most likely cause of this clinical picture?

(A) Chlorpromazine

(**B) Clozapine**

(C) Haloperidol

(D) Risperidone

(E) Thioridazine

Clozapine atypical antipsychotic with most dangerous

Indicate True or false and explain your answer

Chlorpromazine (1 administration produces severe hypotension, tachycardia and .galactorrhea

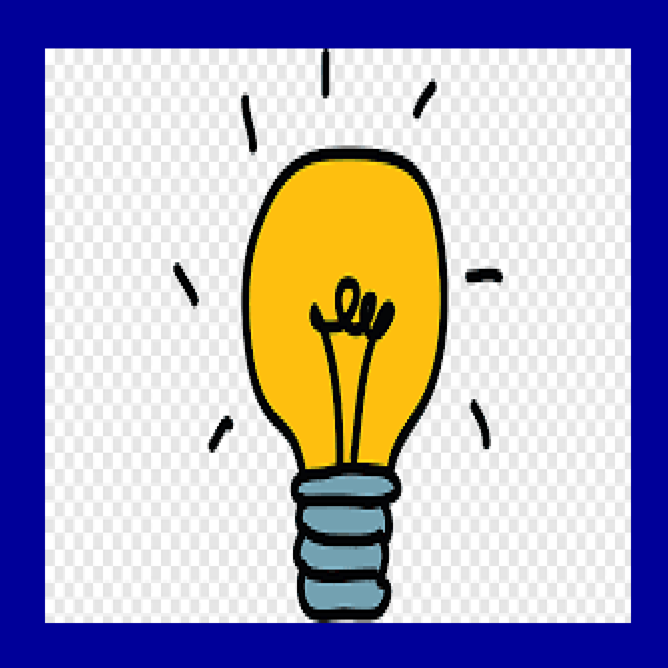
2) Treatment with haloperidol improves the symptoms of parkinsonism.

Droperidol must be added (3 to fentanyl in IV .neurolept analgesia

4) Clozapine is preserved for the refractory patients of Psychosis.

5) The antipsychotic effect of the neuroleptic drug is mediated through blocking of the central D2 receptors only.

Remember



- Most of Anti-psychotics especially 1st generation act via Blocking central D_2 receptor in hypothalamus and limbic system
- The second generation antipsychotics (the a typical group) are week D2 blockers and they act on different serotonergic

Keep in mind that the extrapyramidal manifestations linked to the anti-dopamnergic effects is common in the typical antipsychotic drugs like chlorpromazine and haloperidol .

And less common in the a typical group like clozapine, aripeprazole

SUGGESTED TEXTBOOKS



1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2. Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.


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